a.) Amendment to the Specification:

Please amend the paragraph at page 19, lines 17-22 to read as follows.

Any CH in the CDR-grafted antibody can be used, so long as it belongs to hIg. Preferably, an hIgG class, and any one of γ1, γ2, γ3 and γ4 subclasses belonging to hIgG can be used. Also, any CL of the human ~~chimeric~~ CDR-grafted antibody can be used, so long as it belongs to hIg, and those of κ class or λ class can be used.

Please amend the paragraph starting at page 20, line 6 and ending at page 23, line 24 to read as follows.

Among these human CDR-grafted antibodies ~~compositions~~, preference is given to a human CDR-grafted antibody wherein the VH of the antibody comprises an amino acid sequence selected from amino acid sequences in which at least one amino acid selected from 1st position Gln, 11th position Val, 42nd position Gly, 75th position Ser, 77th position Asn, 84th position Asn, 93rd position Val, 97th position Ala, and 98th position Arg in the amino acid sequence represented by SEQ ID NO:11 is substituted and amino acid sequences in which at least one amino acid selected from 49th position Ser, 77th position Asn, 84th position Asn, 93rd position Val, 97th position Ala, and 98th position Arg in the amino acid sequence represented by SEQ ID NO:54 is substituted; a human CDR-grafted antibody wherein the VL of the antibody comprises an amino acid sequence selected from amino acid sequences in which at least one amino acid selected from 4th position Met,9th position Asp, 10th position Ser, 11th position Leu, 15th position Leu, 22th position Asn, 35th position Tyr, 39th position Pro, 42th position Pro, 45th position Leu, 46th position Leu, 69th position Asp, 70th position Phe, 71st position Thr,

82nd position Val, and 84th position Val in the amino acid sequence represented by SEQ ID NO:14 is substituted and amino acid sequences in which at least one amino acid selected from 4th position Met, 9th position Ser, 10th position Ser, 11th position Leu, 15th position Val, 35th position Tyr, 39th position Pro, 42nd position Ala, 45th position Leu, 46th position Leu, 69th position Asp, 70th position Phe, 71st position Thr, and 82nd position Phe in the amino acid sequence represented by SEQ ID NO:55 is substituted; and a human CDR-grafted antibody wherein the VH of the antibody comprises an amino acid sequence selected from amino acid sequences in which at least one amino acid selected from 1st position Gln, 11th position Val, 42nd position Gly, 75th position Ser, 77th position Asn, 84th position Asn, 93rd position Val, 97th position Ala, and 98th position Arg in the amino acid sequence represented by SEQ ID NO:11 is substituted and amino acid sequences in which at least one amino acid selected from 49th position Ser, 77th position Asn, 84th position Asn, 93rd position Val, 97th position Ala, and 98th position Arg in the amino acid sequence represented by SEQ ID NO:54 is substituted and wherein the VL of the antibody comprises an amino acid sequence selected from amino acid sequences in which at least one amino acid selected from 4th position Met,9th position Asp, 10th position Ser, 11th position Leu, 15th position Leu, 22th position Asn, 35th position Tyr, 39th position Pro, 42th position Pro, 45th position Leu, 46th position Leu, 69th position Asp, 70th position Phe, 71st position Thr, 82nd position Val, and 84th position Val in the amino acid sequence represented by SEQ ID NO:14 is substituted and amino acid sequences in which at least one amino acid selected from 4th position Met, 9th position Ser, 10th position Ser, 11th position Leu, 15th position Val, 35th position Tyr, 39th position Pro, 42nd position Ala, 45th position Leu, 46th position Leu, 69th position

Asp, 70th position Phe, 71st position Thr, and 82nd position Phe in the amino acid sequence represented by SEQ ID NO:55 is substituted. More preferable human CDR-grafted antibodies include a human CDR-grafted antibody wherein the VH of the antibody comprises an amino acid sequence in which at least one amino acid selected from 1st position Gln, 11th position Val, 42nd position Gly, 75th position Ser, 77th position Asn, 84th position Asn, 93rd position Val, 97th position Ala, and 98th position Arg in the amino acid sequence represented by SEQ ID NO:11 is substituted and wherein the VL of the antibody comprises an amino acid sequence in which at least one amino acid selected from 4th position Met,9th position Asp, 10th position Ser, 11th position Leu, 15th position Leu, 22th position Asn, 35th position Tyr, 39th position Pro, 42th position Pro, 45th position Leu, 46th position Leu, 69th position Asp, 70th position Phe, 71st position Thr, 82nd position Val, and 84th position Val in the amino acid sequence represented by SEQ ID NO:14 is substituted; and a human CDR-grafted antibody wherein the VH of the antibody comprises an amino acid sequence in which at least one amino acid selected from 1st position Gln, 11th position Val, 42nd position Gly, 75th position Ser, 77th position Asn, 84th position Asn, 93rd position Val, 97th position Ala, and 98th position Arg in the amino acid sequence represented by SEQ ID NO:11 is substituted and wherein the VL of the antibody comprises an amino acid sequence in which at least one amino acid selected from 4th position Met, 9th position Ser, 10th position Ser, 11th position Leu, 15th position Val, 35th position Tyr, 39th position Pro, 42nd position Ala, 45th position Leu, 46th position Leu, 69th position Asp, 70th position Phe, 71st position Thr, and 82nd position Phe in the amino acid sequence represented by SEQ ID NO:55 is substituted; a human CDR-grafted antibody wherein the VH of the antibody comprises an amino acid sequence in which at

least one amino acid selected from 49th position Ser, 77th position Asn, 84th position Asn, 93rd position Val, 97th position Ala, and 98th position Arg in the amino acid sequence represented by SEQ ID NO:54 is substituted and wherein the VL of the antibody comprises an amino acid sequence in which at least one amino acid selected from 4th position Met,9th position Asp, 10th position Ser, 11th position Leu, 15th position Leu, 22th position Asn, 35th position Tyr, 39th position Pro, 42th position Pro, 45th position Leu, 46th position Leu, 69th position Asp, 70th position Phe, 71st position Thr, 82nd position Val, and 84th position Val in the amino acid sequence represented by SEQ ID NO:14 is substituted; and a human CDR-grafted antibody wherein the VH of the antibody comprises an amino acid sequence in which at least one amino acid selected from 49th position Ser, 77th position Asn, 84th position Asn, 93rd position Val, 97th position Ala, and 98th position Arg in the amino acid sequence represented by SEQ ID NO:54 is substituted and wherein the VL of the antibody comprises an amino acid sequence in which at least one amino acid selected from 4th position Met, 9th position Ser, 10th position Ser, 11th position Leu, 15th position Val, 35th position Tyr, 39th position Pro, 42nd position Ala, 45th position Leu, 46th position Leu, 69th position Asp, 70th position Phe, 71st position Thr, and 82nd position Phe in the amino acid sequence represented by SEQ ID NO:55 is substituted.

Please amend the paragraph at page 44, lines 10-12 to read as follows.

Antibody fragment can be prepared by genetic engineering techniques or protein chemical techniques based on the anti-hIGF antibody mentioned in the above 1 ~~and 2~~.

Please amend the paragraphs starting at page 45, line 25 and ending at page 48, line 12 to read as follows.

$F(ab')_2$ can be prepared by treating of IgG with protease, pepsin by using protein chemical techniques. After the treatment with pepsin, it can be recovered as a uniform $F(ab')_2$ by the same purifying operation as in the case of Fab (Monoclonal Antibodies: Principles and Practice, third edition, Academic Press, 1995). It can also be prepared by a method where Fab' mentioned in the ~~following 3(3)~~ following 2(3) is treated with a maleimide such as o-PDM or bismaleimide to form a thioether bond or by a method where it is treated with DTNB [5,5'-dithiobis(2-nitrobenzoic acid)] to form an S-S bond (Antibody Engineering, A Practical Approach, IRL Press, 1996).

(3) Preparation of Fab'

Fab' can be prepared by treating $F(ab')_2$ mentioned in the ~~above 3(2)~~ above 2(2) with a reducing agent such as dithiothreitol. Fab' can be prepared by genetic engineering techniques using *E. coli* in many cases or using insect cells, animal cells, and the like. For example, DNA encoding V region of the antibody mentioned in the above 2(2), 2(4) and 2(5) is cloned to a vector for expression of Fab' whereupon Fab' expression vector can be prepared. With regard to a vector for expression of Fab', any vector may be

used so long as DNA for Fab' can be inserted and expressed. Fab' can be formed and accumulated in an inclusion body or a periplasmic space by introducing the Fab' expression vector into an appropriate *E. coli*. From the inclusion body, active Fab' can be obtained by a refolding method which is usually used in proteins and, when the Fab' is expressed in the periplasmic space, it can be recovered extracellulary by disrupting the cell with treating such as partial digestion by lysozyme, osmotic shock and sonication. After the refolding or from the disrupted cell solution, a uniform Fab' can be purified using a protein G column or the like (Antibody Engineering, A Practical Approach, IRL Press, 1996).

(4) Preparation of scFv

scFv can be prepared using phage or E. coli or using insect cells or animal cells by genetic engineering techniques. For example, DNA encoding V region of the antibody mentioned in the above 2(2), 2(4) and 2(5) is cloned to a vector for expression of scFv whereupon an scFv expression vector can be prepared. With regard to the vector for expression of scFv, any vector may be used so long as the DNA of scFv can be inserted and express. Examples thereof are pCANTAB5E (manufactured by Pharmacia), pHFA (Human Antibodies & Hybridomas, 5, 48, 1994), and the like. When scFv expression vector is introduced into an appropriate E. coli and a helper phage is infected, to thereby obtain a phage which expresses scFv on the phage surface in a fused form with the surface protein of the phage. Also, scFv can be formed and accumulated in a periplasmic space or an inclusion body of E. coli into which scFv expression vector is introduced. From the inclusion body, active scFv can be obtained by a refolding method generally used for proteins and, when scFv is expressed in the periplasmic space, it can be recovered

extracellulary by disrupting the cell with treating such as partial digestion by lysozyme, osmotic shock and sonication. After the refolding or from the disrupted cell solution, a uniform scFv can be purified using a cation-exchange chromatography or the like (Antibody Engineering, A Practical Approach, IRL Press, 1996).

(5) Preparation of diabody

Diabody can be prepared using E. coli in many cases or using insect cells, animal cells, and the like by genetic engineering techniques. For example, DNAs in which VH and VL of the antibody mentioned in the above 2(2), 2(4) and 2(5) are linked by a linker coding 8 amino acid residues or less is prepared and cloned into a vector for expression of diabody whereupon a diabody expression vector can be prepared. With regard to a vector for expression of diabody, any vector may be used so long as the DNA of diabody can be inserted and expressed. Examples thereof are pCANTAB 5E (manufactured by Pharmacia) and pHFA (Human Antibodies Hybridomas, 5, 48, 1994). Diabody can be formed and accumulated in a periplasmic space or an inclusion body of E. coli into which a diabody expression vector is introduced. From the inclusion body, active diabody can be obtained by a refolding method generally used for proteins and, when the diabody is expressed in the periplasmic space, it can be recovered extracellulary by disrupting the cell with treating such as partial digestion by lysozyme, osmotic shock and sonication. After the refolding or from the disrupted cell solution, a uniform ~~scFv~~ diabody can be purified using a cation-exchange chromatography or the like (Antibody Engineering, A Practical Approach, IRL Press, 1996).

Please amend the paragraph at page 49, lines 20-28 to read as follows.

The binding activity of an anti-hIGF humanized antibody to hIGF in a culture supernatant or the binding activity of the purified anti-hIGF humanized antibody to hIGF can be measured by ELISA, biosensor Biacore and the like. Additionally, the activity of the antibody of the present invention to inhibit the hIGF functions can be measured by examining the influence of the antibody upon the in vivo or in vitro proliferation of a cell line showing hIGF-dependent proliferation ~~as shown above in 1.(7)~~.

Please amend the paragraph at page 53, lines 12-17 to read as follows.

~~The anti-hIGF antibody and the antibody fragment thereof of the present invention can be administered as it is, but it is desirable in general to provide it as a pharmaceutical preparation produced by an optional method well known in the technical field of manufacturing pharmacy, by mixing it with one or more pharmacologically acceptable carriers.~~

Please amend the paragraph starting at page 64, line 26 and ending at page 65, line 17 to read as follows.

Using pBS/CamHV0 obtained in Example 1(2) as a template and also using the synthetic oligo-DNA represented by SEQ ID NO:38 and the synthetic oligo-DNA represented by SEQ ID NO:39, a 5'-QG gene fragment of about 250 bp was amplified by PCR in the same manner as described in above (3-1); and also using the synthetic oligo-DNA represented by SEQ ID NO:40 and the synthetic oligo-DNA represented by SEQ ID

NO:41, a 3′-GAR gene fragment of about 250 bp was amplified by PCR in the same manner as described in above (3-1). The aimed gene fragments were recovered by fractionation by 1.5 % agarose gel electrophoresis. Using each gene fragment recovered, the T3 primer at the 5′-terminal of the 5′-QG gene fragment (manufactured by Takara Bio) and the T7 primer at the 3′-terminal of the 3′-GAR gene fragment (manufactured by Takara Bio), PCR was carried out in the same manner as described ~~above (3-2)~~ above (3-1). After the reaction, the reaction solution was fractionated by 1.5 % agarose gel electrophoresis in the same manner as in Example 1(2), to recover gene fragment of about 500 bp. The recovered gene fragment was cloned into pBS, to obtain an aimed plasmid pBS/QGAR comprising cDNA represented by SEQ ID NO:18, which encodes the amino acid sequence QGAR represented by SEQ ID NO:26.

Please amend the paragraph starting at page 105, line 23 and ending at page 106, line 24 to read as follows.

Firstly, in order to insert the cDNAs for the VH and VL of KM1468 into the expression vector pKANTEX93 such that the amino acid sequences are not changed, cDNAs for the VH and VL of KM1468 were reconstructed by PCR. As the primers, synthetic DNAs respectively having the nucleotide sequences of SEQ ID NOS:68 and 69 were designed for the VH cDNA, and synthetic DNAs respectively having the nucleotide sequences of SEQ ID NOS:70 and 71 were designed for the VL cDNA. Each of the synthetic DNAs contains a restriction enzyme recognizing sequence in the 5'-terminal for its cloning into pKANTEX93. Specifically, 20 ng of the plasmid pKM1468H5-2 obtained in Reference Example 5 (3) was added to a buffer solution containing 50 μl of KOD DNA

Polymerase-attached PCR Buffer #1 (manufactured by TOYOBO), 0.2 mM dNTPs, 1 mM magnesium chloride and 0.5 μM of the synthetic DNAs having the nucleotide sequences shown in ~~SEQ ID NOS:67 and 68~~ SEQ ID NOS:68 and 69, and using a DNA thermal cycler GeneAmp PCR System 9600 (manufactured by PERKIN ELMER), the mixture was heated at 94°C for 3 minutes, to which 2.5 units of KOD DNA Polymerase (manufactured by TOYOBO) was added, and a cycle of 15 seconds at 98°C, 2 seconds at 65°C and 30 seconds at 74°C was repeated 25 cycles. In the same manner, another PCR was carried out by the same method described in the above, by adding 20 ng of the plasmid pKM1468L5-1 obtained in Reference Example 5 (3) to a buffer solution containing 50 μl of KOD DNA Polymerase-attached PCR Buffer #1 (manufactured by TOYOBO), 0.2 mM dNTPs, 1 mM magnesium chloride and 0.5 μM of the synthetic DNA fragments having the nucleotide sequences shown in ~~SEQ ID NOS:69 and 70~~ SEQ ID NOS:70 and 71. A 10 μl portion of each reaction solution was subjected to an agarose gel electrophoresis, and then a PCR product of about 0.5 kb for VH or a PCR product of about 0.43 kb for VL was recovered using QIAquick Gel Extraction Kit (manufactured By QIAGEN).